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PRINCIPAL INVESTIGATOR: Seong K. Mun, PhD

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Seong K. Mun, Linda Larson-Prior, Kenneth Wong, Alpay Ozcan

E-Mail:munsk@vt.edu

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14. ABSTRACT
We have designed an appropriate PET imaging protocol that will allow us to differentiate regional metabolic activity between different sleep cycle periods. Pilot diffusion MRI data using phantoms has informed a new and more accurate mathematical model, CFD-MRI, for MR tractography. The analysis indicates the necessity of further investigations for better understanding and quantifying various artifacts in data collection. Using the simultaneous fMRI-EEG data techniques, brain regions of interest and their activity has been identified. The results of these studies clearly indicate changes in resting state brain network connectivity in the transition from alert wakefulness to sleep.

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Neuroperformance, Sleep cycle, metabolism, thalamic structures, PET Imaging, MR Imaging, functional MRI, electroencephalography (EEG)

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Introduction

Sleep restriction and deprivation have profound negative effects on cognitive ability and task performance (e.g., vigilance). At the same time, physical and psychological stressors often lead to sleep disruptions, which compromise the body's ability to reap the restorative benefits of sleep. Military personnel often suffer from decreased **quality** and **quantity** of sleep, increasing their susceptibility to a host of neurological problems and limiting their ability to perform the challenging mental tasks that their missions require. Further, the effects of pharmacological interventions aimed at ameliorating the deleterious effects of both sleep loss and mental and physical stress are only poorly understood and may result in unanticipated long-term effects in those serving under combat conditions. Advances in imaging technology have enabled human studies of neurochemistry, energy metabolism and functional brain networks that were previously impossible.

Our research uses a combination of human imaging-based studies to advance our fundamental knowledge of the effects of sleep and sleep-related stressors on neuroperformance. In order to achieve this goal, the team utilizes ultra-high resolution imaging hardware, 7T MRI scanner and High Resolution PET (HRRT) scanner in tandem. These scanners at Neuroscience Research Institute at Gachon University are conveniently positioned so to be linked by a patient tray system, unique around the world, that can carry the subject from one scanner to the other, thereby keeping the reference frames of each modality intact and physically registered. The removal of software image registration from data analysis, as well as prevention of signal loss by the absence of physical/electrical interactions between the devices results in unprecedented high quality, ultra-high resolution images.

Adding this unique high precision setup to our capabilities, the scope of this research is to 1) use PET/MRI studies to understand glucose metabolism and dopamine binding in the brain, particularly in the brainstem and thalamus; 2) EEG/fMRI studies focusing on the functional connectivity of networks between the thalamus and cortex that control the descent into sleep and are altered by sleep deprivation; 3) EEG/fMRI studies designed to improve our understanding of the interaction between sleep loss, emotional stress and cognitive function, and 4) Development of reference image databases for high field MRI studies of the brain.

Body

The research accomplishments associated with each task outlined in the approved Statement of Work for year 1 are as follows:

A. PET/MRI studies of brainstem and cortex sleep regulation

A1. Provide sleep neuroscience expertise to the Neuroscience Research Institute (NRI) of Gachon University for PET/MRI studies.

A1.1. Training in the Neurobiology of Sleep and Sleep Medicine was provided by Dr. Larson-Prior. Since Fall 2012, NRI of Gachon University is capable of conducting experiments with no or minimal assistance from Dr. Larson-Prior.

A2. Analysis of pre-existing, de-identified PET/MRI data.

A2.1. Drs. Gates and Özcan are leading an effort to segment brain regions using anatomical 7T images. Dr. Larson-Prior offered guidance on the regions to select and offered resources for segmenting the brain based on anatomical landmarks in the 7T images as opposed to PET functional data. This approach offers a potential improvement upon the current standard, which is to identify regions using normed atlases or results from the functional PET data. Under their supervision, a neuroscience graduate student has 1) segmented 10 regions of the hippocampus using anatomical features in the 7T images to create a mask, 2) registered the 7T images of the hippocampus to the PET images, and 3) extracted the PET data for each individual in the 10 regions using the masks. Efforts are continuing to extract PET data from the thalamus, hypothalamus, and brain stem regions in a similar manner.

Dr. Mun and Dr. Gates visited Gachon University between June 22-28, 2013 to discuss the progress on data analysis. As AIC and Gachon University took complementary approaches to data processing it has been agreed that further data on the mid-brain sections will be transferred from Gachon to continue the analysis with two different approaches.

A major issue that has been encountered is the normalization of PET signal. Whereas Gachon team is taking a manual approach for identifying white matter regions, AIC is focused on automated co-registration algorithms to achieve the same goal. The reproducibility and accuracy of each method will be tested. Early analysis indicates that it might be necessary to adopt a hybrid approach, which will steer manually the automated algorithms towards an accurate solution.

Dr. Larson-Prior is leading preparation of a manuscript detailing results of the PET/MRI data from initial studies using FDG-PET in human subjects where the brainstem raphe nuclei were imaged. Analysis of thalamic and hippocampal activity during slow wave sleep and REM sleep continues, and will be the focus of a manuscript which Dr. Young is preparing.

A3. Collaborative development of new data processing and analysis methods.

A3.1. *Diffusion MRI:*

Dr. Özcan hosted a research topic for exploring different techniques including but not limited to diffusion MRI to explore white matter integrity. The research topic appeared on the open access Frontiers in Physiology, Integrative Neuroscience. The last article was published on 14 May 2013. The following is the list of articles from different institutions that have been published on the Research Topic:

Original Research Article, Published on 06 Mar 2013
Probing white-matter microstructure with higher-order diffusion tensors and susceptibility tensor MRI
Chunlei Liu, Nicole E. Murphy and Wei Li
doi: 10.3389/fnint.2013.00011

Original Research Article, Published on 01 Feb 2013
Quantification of anisotropy and fiber orientation in human brain histological sections
Matthew D. Budde and Jacopo Annese
doi: 10.3389/fnint.2013.00003

Original Research Article, Published on 14 May 2013
Using diffusion anisotropy to characterize neuronal morphology in gray matter: the orientation distribution of axons and dendrites in the NeuroMorpho.org database
Mikkel B. Hansen, Sune N. Jespersen, Lindsey A. Leigland and Christopher D. Kroenke
doi: 10.3389/fnint.2013.00031

Mini Review Article, Published on 11 Mar 2013
What does anisotropy measure? Insights from increased and decreased anisotropy in selective fiber tracts in schizophrenia
L. M. Alba-Ferrara and Gabriel A. de Erausquin
doi: 10.3389/fnint.2013.00009

Hypothesis & Theory Article, Published on 11 Apr 2013
Probing myelin and axon abnormalities separately in psychiatric disorders using MRI techniques
Fei Du and Dost Öngür
doi: 10.3389/fnint.2013.00024

Original Research Article, Published on 02 Apr 2013
Complete fourier direct magnetic resonance imaging (CFD-MRI) for diffusion MRI
Alpay Özcan
doi: 10.3389/fnint.2013.00018

Original Research Article, Published on 13 Mar 2013
Axonal and glial microstructural information obtained with diffusion-weighted magnetic resonance spectroscopy at 7T
Itamar Ronen, Ece Ercan and Andrew Webb

doi: 10.3389/fnint.2013.00013

The research topic is essential for understanding changes in the white matter and MRI's limits to measure these changes, an understanding that will be critical to studies in which prolonged sleep deprivation leads to neurostress. Further understanding of the biological and micro-structural changes within the white matter using alternative techniques proposed in the topic will potentially be obtained. By identifying the brain regions that are most affected, the assessment of how much the warfighters are affected during and after return from active duty might be possible. The methods proposed in the topic have common goals including the detection of traumatic brain injury (TBI) and its effects on brain tissue.

A4. Recruit new subjects for studies of normal sleep using FDG and raclopride.

Recruitment of new subjects is deferred until the funding arrangements are finalized.

B. Studies of thalamo-cortical network function during sleep

B1. Analysis of pre-existing EEG/fMRI data on N1 and N2 sleep to determine changes in thalamo-cortical network connectivity in the descent to sleep.

B1.1 *EEG/fMRI studies of sleep in normal human subjects.*

B2. Data collection and analysis to (1) increase the number of subjects reaching N2 sleep, and (2) collect data from subjects reaching N3 sleep.

All IRB protocols have been approved. Data collection is dependent upon continued funding of the project.

B3. Collect normative data on cognitive vigilance (PVT) prior to and following sleep (task flanks sleep) to analyze thalamo-cortical network interactions.

All IRB protocols have been approved. Data collection is dependent upon continued funding of the project.

C. Assemble and annotate a reference dataset of 7T brain images.

Dr. Özcan has completed the preparation of a 3D tractography atlas obtained from the Diffusion MRI data acquired at Gachon University using Tract Density Imaging method. The atlas has color coded views of tracts according to their orientations. There are three atlases formed from transversally, sagittally and coronally oriented acquisitions. Furthermore, each atlas has two versions: 1-Isosurfaces presenting the tracts constructed using the full triangulation. These are larger data sets with high fidelity. 2-Isosurfaces obtained after compactifying the surfaces. In this case the points that belong to the same plane are taken out of the triangles thereby reducing the file size. The atlases can be visualized using open source software Paraview from KitWare.

Preparations in Anticipation of Future Data Collection and Analysis

Dr. Larson-Prior and Ms. Nolan have continued work programming presentation protocols in EPrime-Pro 2.0. This has included scientific discussions with colleagues on the image files that are most appropriate to the task and on the duration and number of experimental runs to be collected. Initial programming has been focused on behavioral and EEG data acquisition. Initial studies will include behavioral pilot studies to test the efficacy and reliability of the stimulus protocols proposed in this study. Following pilot testing, stimuli will be programmed for fMRI acquisition.

The IT infrastructure that will provide data storage, analysis using computational methods and facilitate communication between different centers of the project in a secure manner has been implemented at the Arlington Innovation Center. The network consists of a firewall and VPN device. Whereas publicly available information are presented at AIC webserver (Dell PowerEdge R310, 4 core Intel® Xeon® X3470, 16Gb memory, 4Tb raid 5 disk capacity), the collaborators in the project have the ability to access their data over a secure VPN connection on the computational server (Dell PowerEdge T710, 8 core Intel® Xeon® X5647, 96Gb memory, 14Tb raid 5 disk space) that is protected behind AIC firewall. The firewall and VPN services are provided by a Cisco ASA5520 appliance and Cisco 2960 switch. A beta version of in-house developed collaborative platform that allows the collaborators to drop and annotate data, manuscripts, presentations and documents have also been installed on the storage server. The platform will speed up data analysis and development of new ideas.

Key Research Accomplishments

- IRB process was completed on July 1st, 2013 upon obtaining approval from Washington University in St. Louis (30 May 2013), Virginia Tech (1March 2013) and Army HRPO.
- A 3D diffusion MRI based tractrography atlas has been completed.
- HRRT-PET and 7.0T MRI data have been acquired for 19 subjects during wake, slow wave sleep and REM sleep at the Gachon University Neuroscience Research Institute. Data analysis centered on the changes in metabolic activity in the brainstem raphe nuclei between neural states based on FDG-PET imaging, and a manuscript reporting the results of these studies is currently in preparation.

Reportable Outcomes

Manuscripts,

- Hillary, F. G., Medaglia, J. D., Gates, K. M., & Molenaar, P. C. M. (In Press). Effective connectivity changes after task practice in traumatic brain injury: Application of extended unified structural equation modeling. Brain Imaging and Behavior.
- Adriene M. Beltz, Kathleen M. Gates, Anna S. Engels, Peter C.M. Molenaar, Carmen Pulido, Robert Turrisi, Sheri A. Berenbaum, Rick O. Gilmore, Stephen J. Wilson, Changes in alcohol-related brain networks across the first year of college: A prospective pilot study using fMRI effective connectivity mapping, Addictive Behaviors, Volume 38, Issue 4, April 2013, Pages 2052-2059
- Iyer, S., Shafran, I., Grayson, D., Gates, K.M., Nigg, J., & Fair, D. (Under Review). Applying Bayesian principles based PC algorithm to characterize the effects of connectivity and resting state fMRI data. NeuroImage.
- Karunanayaka, P., Weitekamp, C. W., Gates, K. M., Wang, J., Eslinger, P. J., Molenaar, P. C. M., & Yang, Q. X. (Under Review). Dynamic behavior of BOLD signal and the associated olfactory neural networks: A functional magnetic resonance imaging study. Human Brain Mapping.
- Nichols, T., Gates, K.M., Molenaar, P. C. M., & Wilson, S. J. (Under Review). BOLDer but more efficient: Patterns of brain activation and effective connectivity associated with better cognitive performance in nicotine-deprived smokers. Addiction Biology.
- Dr. Özcan published the manuscript titled Complete fourier direct magnetic resonance imaging (CFD-MRI) for diffusion MRI in *Frontiers in Integrative Neuroscience* titled, "New Models of Diffusion Weighted MRI Signal and Alternative Methods for Characterization of White Matter Integrity" (see also the appendix)

Abstracts

- L. J. Larson-Prior, Y.D. Son, E.J. Choi, J.H. Kim, S.I. Hwang, S.Y. Lee, Y.B. Kim, S.K. Mun and Z. H. Cho, Brainstem regulation of sleep and waking: a PET/MRI perspective, Organization for Human Brain Mapping in June, 2013, Seattle, USA
- Kathleen Gates, Peter Molenaar, Joel Nigg, Damien Fair, Data-driven approach for identifying subgroups using resting-state fMRI, Organization for Human Brain Mapping in June, 2013, Seattle, USA
- Gates, K. M. (October, 2012). Identifying subgroups using fMRI connectivity maps. Paper presented at the annual meeting for the Society for Neuroscience, New Orleans, LA.

Presentations:

- Dr. Larson-Prior presented a paper at the Organization for Human Brain Mapping in June, 2013 entitled, "Brainstem regulation of sleep and waking: a PET/MRI perspective" which will form the basis of a full manuscript on this completed project using FDG-PET imaging of the human brainstem during sleep
- Dr. Gates presented a paper at the Organization for Human Brain Mapping in June, 2013. The paper was entitled, "Data-driven approach for identifying subgroups using resting-state fMRI".
- Dr. Özcan was an invited speaker at the Program on Pediatric Imaging and Tissue Sciences (PPITS), Eunice Kennedy Shriver National Institute of Child Health & Human Development, National Institutes

of Health, on 31 Oct. 2012. This is the laboratory under the direction of Dr. Pierpaoli and Dr. Basser where diffusion tensor imaging was invented. Dr. Özcan presented the new model Complete Fourier Direct MRI.

- Dr. Özcan was also invited to Image Processing Core, Center for Neuroscience and Regenerative Medicine, Clinical Center of the National Institutes of Health on 13 November 2012 to give a talk on white matter integrity and diffusion MRI.

Conclusion

The analysis of previously collected pilot diffusion MRI data from a fixed human brain showed that there are significant challenges for adopting CFD-MRI to 7T imaging. First and foremost, it will be necessary to understand phase artifacts for the higher dimensional CFD-MRI. The point spread function (PSF) corrections utilized at Gachon University needs to be modified or an alternative method including more complex modeling of phase artifacts developed in order to apply CFD-MRI to MR acquisition for tractography. More data collection requires more experiments with longer durations, which constitutes a significant challenge for the available resources. Potentially, deeper understanding of anatomy and white matter connectivity will lay the foundation of metabolic and dynamic functional changes within the brain. The microstructural form described by the diffusion MRI is necessary for a complete understanding of brain function. However, theoretical and practical challenges must be addressed in the future to achieve this complex task.

Using simultaneous fMRI-EEG techniques, changes in large-scale network activity in the human brain have been identified based on resting state connectivity measures in the transition from alert wakefulness to sleep. An important change lay in the relationship between the default mode network and two networks involved in attending to and interacting with external stimuli. However, changes in subcortical-cortical connections have been less well defined despite a substantial body of data indicating that these changes do occur. While normal sleep is accompanied by clear substate-dependent changes in cortical network composition, no information is currently available on the changss that accompany abnormal sleep the has been affected by strong emotional and physical stress – conditions that are clearly present under battlefield conditions. While the studies proposed here only mimic those stresses, they would provide valuable, even essential, information on the relationship between sleep need and neural stress that could inform not only optimal sleep durations and therapies under acute stress conditions, but therapeutic solutions to warfighters returning from the battlefield.

"So What" Section:

The outcomes of this Neuroperformance project, which is built on convergence of different disciplines, will have significant implications not only for warfighters but also the general population. Specifically our multi-modal approach, including structural information based on high resolution (7T MRI) anatomical images and diffusion MRI tractography (with information on white matter integrity) and functional information including metabolic activity (via PET), BOLD activity (via fMRI) and electrical activity (via EEG), are essential to neuro-biologically informed approach to improvements in neuroperformance under conditions of restricted sleep and high stress. In addition to improving our understanding of the effects of stress and sleep loss on neuroperformance, and to providing a firmer understanding of the effects of pharmacological interventions under these conditions, these studies will provide novel data on the multifactorial impact of sleep loss, stress and cognitive load in the development of neuropsychiatric disorders commonly associated with abnormalities of sleep such as depression and anxiety.

Appendices

Abstract OHBM 2013, June, 2013, Seattle, USA:

Title: Brainstem regulation of sleep and waking: a PET/MRI perspective

Authors: L. J. Larson-Prior[1,2], Y.D. Son[3], E.J. Choi[3], J.H. Kim[3], S.I. Hwang[3], S.Y. Lee[3], Y.B. Kim[3], S.K. Mun[4] and Z. H. Cho[3]

Affiliations: [1]Department of Radiology, Washington University, St. Louis, MO, USA;

[2]Department of Neurology, Washington University, St. Louis, MO, USA; [3]Neuroscience Research Institute, Gachon University, Incheon, South Korea; Arlington Center for Innovation, Virginia Polytechic Institute & State University, Arlington, VA, USA

INTRODUCTION

During sleep, the brainstem participates in control of the ultradian rhythm cycling between deep slow wave sleep (SWS) and rapid eye-movement (REM) sleep. At present, our understanding of the control mechanisms responsible for this rhythm is based on a large number of animal studies. We present here the first study of changes in glucose metabolism in human brainstem nuclei during normal sleep.

METHODS

Data was collected in 19 healthy young adult subjects under a research protocol approved by the Gachon University IRB. At the time written informed consent was provided, subjects also filled out questionnaires on their normal sleep habits (Pittsburgh sleep quality index, PSQI) and Epworth Sleepiness Scale (ESS), and mood (Beck Depression Inventory, BDI). Subjects participated in a two-day imaging protocol. Imaging on the first day was conducted during quiet wake and consisted of a 30 min uptake period (^{18}F-FDG, 5 mCi) followed by high-resolution research tomography (HRRT)-PET (30 min) and immediately thereafter by 7T-MRI scanning (45 min). Imaging was accomplished using a unique custom-designed PET/MRI system housed Gachon University[1,3]. Subjects then slept in the laboratory, instrumented for polysomnographic recording (PSG) of their sleep. Sleep was scored using standard techniques[2]. On the second day, subjects arrived at 17:00 and participated in MRI (1.5T) and CT scanning. At 22:00 subjects were instrumented for the sleep study. Sleep was monitored, and once the subject reached stable slow wave sleep (SWS, 9 subjects) or stable rapid eye movement (REM, 10 subjects) sleep, FDG injection was initiated. Following a 30 minute uptake period, subjects were wakened and moved to the PET scanner (30 min) followed by MRI scanning (60 min). Following scanning, subjects were allowed to go back to sleep for the remainder of the night.

Data analysis was performed as previously described[3], with the exception that standard uptake value ratios (SUVRs) were obtained by normalization to white matter as changes related to sleep were observed in the cerebellum. Regions of interest were defined for statistical analysis based on fusion images for each subject and consisted of 5 midline raphe nuclei (R1-5). Statistical comparisons were made between awake and each of two sleep stages (SWS and REM) using paired t-tests.

RESULTS

Normal bedtimes reported by subjects ranged between 22:30-4:00 with an average normal sleep period of 6.97±1.04 hrs. Subjects generally slept well, with an average PSQI of 5.26±1.8, and all subjects slept well during both acclimatization and experimental nights in the laboratory. Two subjects exhibited BDI scores outside the normal range (>10), all others were within normal range (mean 4.16±6).

The focus of these studies was on changes in brainstem nuclei during normal sleep, and on the midline raphe nuclei in particular. Raphe nuclei in mesencephalon (dorsal raphe nucleus (DRN), R1), pons (centralis superior, R2; raphe pontis, R3) and ponto-medullary junction (raphe nuclei magnus (RNM), R4, obscures and pallidus, R5) were identified in our study. Significant reductions in glucose metabolism were seen in all raphe nuclei during SWS ($p<0.01$). However, during REM sleep, no significant change in glucose metabolism was seen in pontine raphe nuclei, nor in the raphe obscures/pallidus. While reductions in glucose metabolism in DRN and RNM did reach significance (R1, $p<0.01$; R4, $p<0.1$), reductions were not as strong as in SWS.

CONCLUSIONS

The midline raphe nuclei provide serotonergic innervations to the mammalian CNS, and contribute to circadian rhythmicity as well as to the ultradian rhythms responsible for sleep architecture. These studies point to a complex role for the raphe nuclei in sleep, with all members of this large reticular complex exhibiting changes in glucose metabolism differentially with sleep stage.

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1. Cho, Z.H., Son, Y.D., Kim, H.K., Kim, K.N., Oh, S.H., Han, J.Y., Hong, I.K., and Kim, Y.B. (2008), "A fusion PET-MRI system with a high-resolution research tomography-PET and ultra-high field 7.0 T-MRI for the molecular-genetic imaging of the brain", Proteomics, vol 8, pp 1302-1329
2. Iber, C., Ancoli-Istael, S., Chesson, A.L.J., Quan, S.F. (2007), "The AASM manual for scoring of sleep and associated events", Wetchester, IL, American Academy of Sleep Medicine.
3. Son, Y.D., Cho, Z.H., Kim, H.K., Choi, E.J., Lee, S.Y., Chi, J.G., Park, C.W., Kim, Y.B. (2012) "Glucose metabolism of the midline nuclei raphe in the brainstem observed by PET-MRI fusion", vol 59, pp 1094-1097.

Poster:

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Brainstem Regulation of Sleep and Waking: a PET/MRI Perspective

Linda Larson-Prior[1,2], Young-Don Son[3], Eun-Jung Choi[3], Jeong-Hee Kim[3], Seok-Il Hwang[3], Sang-Yoon Lee[3], Young-Bo Kim[3], Seong-Ki Mun[4], Zang-Hee Cho[3]

[1]Mallinckrodt Institute of Radiology, Washington University School of Medicine in St. Louis MO; [2]Department of Neurology, Washington University School of Medicine in St. Louis MO, [3]Neuroscience Research Institute, Gachon University, Incheon, Republic of Korea, [4]Virginia Polytechnic Institute and State University, Arlington VA

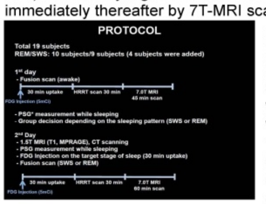
Mallinckrodt Institute of Radiology
Washington University in St. Louis School of Medicine

During sleep, the brainstem participates in control of the ultradian rhythm cycling between deep slow wave sleep (SWS) and rapid eye-movement (REM) sleep. At present, our understanding of the control mechanisms responsible for this rhythm is based on a large number of animal studies. We present here the first study of changes in glucose metabolism in human brainstem nuclei during normal sleep.

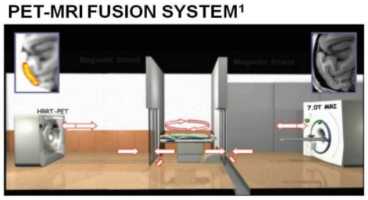
METHODS

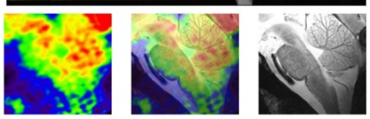
Subjects. Data was collected in 19 healthy young adult subjects (ages 20-28, mean 23.17±2.27) under a research protocol approved by the Gachon University IRB. At the time written informed consent was provided, subjects also filled out questionnaires on their normal sleep habits (Pittsburgh sleep quality index (PSQI) and Epworth Sleepiness Scale (ESS)) and mood (Beck Depression Inventory, BDI).

Protocol. Subjects participated in a two-day imaging protocol. Imaging on the first day was conducted during quiet wake and consisted of a 30 min uptake period (^{18}F-FDG, 5 mCi) followed by high-resolution research tomography (HRRT)-PET (30 min) and immediately thereafter by 7T-MRI scanning (45 min). Imaging was accomplished using a unique custom-designed PET/MRI system housed Gachon University[1,3]. After a short rest period, subjects were instrumented for sleep using a standard montage[2] for an acclimatization night in which they slept in the laboratory while their sleep was monitored. On the second day, subjects arrived at 17:00 and participated in MRI (1.5T) and CT scanning. At 22:00 subjects were instrumented for the sleep study. Sleep was monitored, and once the subject reached stable slow wave sleep (SWS, 9 subjects) or stable rapid eye movement (REM, 10 subjects) sleep, FDG injection was initiated. Following a 30 minute uptake period, subjects were wakened and moved to the PET scanner (30 min) followed by MRI scanning (60 min). Following scanning, subjects were allowed to go back to sleep for the remainder of the night

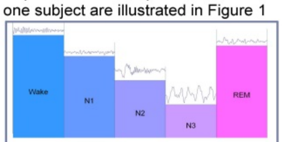


PET-MRI FUSION SYSTEM[1]





Sleep Staging. In both acclimatization and experimental nights, sleep was monitored online and scored using standard techniques[2]. As shown below, sleep is staged based on characteristic changes in scalp-recorded EEG over a full night of sleep. Representative samples of EEG data in one subject are illustrated in Figure 1



One complete sleep cycle contains four stages of sleep, with th initial cycle including a fifth (N1) stage that is not repeated in subsequent cycles. EEG features that define each stage are illustrated above each stage (*LLP, 2009*)

Analysis. Data analysis was performed as previously described[3], with the exception that standard uptake value ratios (SUVRs) were obtained by normalization to white matter as changes related to sleep were observed in the cerebellum. Regions of interest were defined for statistical analysis based on fusion images for each subject and consisted of 5 midline raphe nuclei (R1-5, Figure 2). Statistical comparisons were made between awake and each of two sleep stages (SWS and REM) using paired t-tests.

FIGURE 1

TABLE 1: SUBJECT CHARACTERISTICS

Subject	Sleep (hr)	PSQI	BDI	ESS
SWS001	6	5	3	7
SWS002	7	9	10	5
SWS003	8	6	1	3
SWS004	7.75	9	1	8
SWS005	6	10	11	7
SWS006	7	4	0	5
SWS007	6	3	1	4
SWS008	6	4	1	9
SWS009	6.5	4	1	7
REM001	8	4	7	10
REM002	7.6	4	2	5
REM003	7	4	2	10
REM004	6	6	2	3
REM005	7	7	2	3
REM006	7.5	4	0	9
REM007	10	6	7	7
REM008	6	5	2	9
REM009	7	4	1	2
REM010	6	6	25	8

Nineteen subjects participated in the study protocol detailed in METHODS. All subjects provided information on their normal sleep habits by filling Korean language versions of standard and validated instruments. Table 1 lists the results for each study subject. Table 2 provides normative values by which individual and group results may be assessed.

TABLE 2: NORMATIVE VALUES

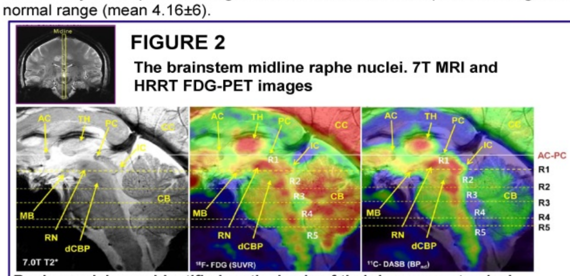
INSTRUMENT	NORMATIVE VALUES
Nighttime sleep	7-9 hrs
PSQI	0- great sleeper 21- severe problems
ESS	0 – wide awake <10 - normal 24 - falling asleep
BDI	1-10 normal 11-16 mild 17- 20 borderline 21-30 moderate 31-40 severe > 40 extreme

RESULTS

Normal bedtimes reported by subjects ranged between 22:30-4:00 with an average normal sleep period of 6.97±1.04 hrs. Subjects generally slept well, with an average PSQI of 5.26±1.8, and all subjects slept well during both acclimatization and experimental nights in the laboratory. Two subjects exhibited BDI scores outside the normal range (>10), all others were within normal range (mean 4.16±6).

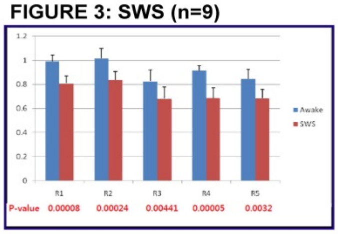
FIGURE 2

The brainstem midline raphe nuclei. 7T MRI and HRRT FDG-PET images



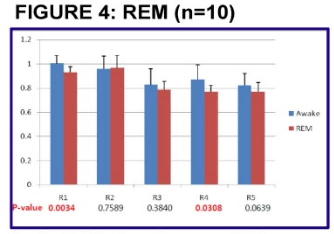
Raphe nuclei were identified on the basis of their known anatomical locations.[3] In addition, as the midline raphe nuclei provide the largest source of serotonergic input to cortex and spinal cord, presence of the 5HTT was also used to verify identification (Cho et al., unpublished).

FIGURE 3: SWS (n=9)



During slow wave sleep, glucose metabolism was significantly reduced in all raphe nuclei in agreement with studies in animal models

FIGURE 4: REM (n=10)



During REM sleep, there was little reduction in glucose metabolism which was only significantly reduced in R1 (DRN) and R4 (raphe magnus)

CONCLUSIONS

The midline raphe nuclei provide serotonergic innervations to the mammalian CNS, and contribute to circadian rhythmicity as well as to the ultradian rhythms responsible for sleep architecture. These nuclei are generally believed to be most active in wake, progressively decrease activity in NREM sleep and be largely silent in REM. Our results are consistent with expectation in NREM but not in REM sleep. It is possible that inclusion of non-serotonergic or atypically activating cells resulted in this difference. Alternatively, these results could reflect species differences in humans relative to felines or rodents in whom most studies of brainstem sleep regulation have been carried out.. Further studies using transmitter radioligands are needed to provide important information on brainstem regulation of sleep in human subjects.

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Complete fourier direct magnetic resonance imaging (CFD-MRI) for diffusion MRI

Alpay Özcan*

Health Research, Arlington Innovation Center, Virginia Polytechnic Institute and State University, Arlington, VA, USA

Edited by:
Elizabeth B. Torres, Rutgers University, USA

Reviewed by:
Bennett A. Landman, Vanderbilt University, USA
Evren Ozarslan, Brigham and Women's Hospital, USA

***Correspondence:**
Alpay Özcan, Health Research, Arlington Innovation Center, Virginia Polytechnic Institute and State University, 900 N. Glebe Road, Arlington, VA 22203, USA.
e-mail: alpay@vt.edu

The foundation for an accurate and unifying Fourier-based theory of diffusion weighted magnetic resonance imaging (DW–MRI) is constructed by carefully re-examining the first principles of DW–MRI signal formation and deriving its mathematical model from scratch. The derivations are specifically obtained for DW–MRI signal by including all of its elements (e.g., imaging gradients) using complex values. Particle methods are utilized in contrast to conventional partial differential equations approach. The signal is shown to be the Fourier transform of the joint distribution of number of the magnetic moments (at a given location at the initial time) and magnetic moment displacement integrals. In effect, the *k*-space is augmented by three more dimensions, corresponding to the frequency variables dual to displacement integral vectors. The joint distribution function is recovered by applying the Fourier transform to the complete high-dimensional data set. In the process, to obtain a physically meaningful real valued distribution function, phase corrections are applied for the re-establishment of Hermitian symmetry in the signal. Consequently, the method is fully unconstrained and directly presents the distribution of displacement integrals without any assumptions such as symmetry or Markovian property. The joint distribution function is visualized with isosurfaces, which describe the displacement integrals, overlaid on the distribution map of the number of magnetic moments with low mobility. The model provides an accurate description of the molecular motion measurements via DW–MRI. The improvement of the characterization of tissue microstructure leads to a better localization, detection and assessment of biological properties such as white matter integrity. The results are demonstrated on the experimental data obtained from an *ex vivo* baboon brain.

Keywords: magnetic resonance imaging, diffusion weighted imaging, fourier transform

1. INTRODUCTION

Since the conception of mathematical models for the effect of the magnetic moment diffusion in nuclear magnetic resonance (NMR) experiments by Hahn (1950), Carr and Purcell (1954), and Torrey (1956), several methods have been proposed for analysis of diffusion-weighted (DW) magnetic resonance imaging (MRI) signal. These advancements endowed with the non-invasive, *in vivo* nature of the technique, have propelled the initial utilization of DW imaging measures, e.g., apparent diffusion coefficient in early detection of ischemia (Moseley et al., 1990; Baird and Warach, 1998), to many highly crucial areas in research and clinical imaging: for example in cancer diagnosis (Song et al., 2002; Turkbey et al., 2009; Xu et al., 2009), follow-up on treatment, pre- and post-operative assessment for different organs [e.g., fiber tracking (Conturo et al., 1999; Mori and van Zijl, 2002)] white matter integrity assessment (Budde et al., 2007; Correia et al., 2008) as in monitoring of neurological diseases such as multiple sclerosis (Song et al., 2002) and disorders (Ciccarelli et al., 2008) like schizophrenia (Seal et al., 2008; Voineskos et al., 2010) and Alzheimer's disease (Mielke et al., 2009), as well as neonatal development (McKinstry et al., 2002) and traumatic brain injury (Mac Donald et al., 2011).

In brief, diffusion weighted magnetic resonance imaging (DW–MRI) has become an indispensable and versatile technique playing an important role in several applications by its ability to estimate diffusion. The abundance of DW–MRI models is an indicator of room for improvement as well as the necessity for unification [see Özcan et al. (2012) for a detailed account of the partial differential equation (PDE) based adaptation's implications as well as a thorough mathematical analysis and a description of the background of existing methods].

DW–MRI's aim is to obtain measures and characterization of microstructure by investigating the diffusion process. Several methods and models have been proposed, all originating from the seminal work of Stejskal and Tanner (1965). Therein, under the influence of the additional motion sensitizing magnetic field gradients, the self-diffusion PDE of the magnetic moments is included in the Bloch PDE to model the attenuation in the DW–NMR spectroscopy signal. The result is the estimation of the *scalar* diffusion coefficient of the entire sample. In a sense, DW–NMR added another dimension, i.e., the *magnetic moment motion*, to the spectroscopic information even before the introduction of *magnetic moment position* later by the invention of MR imaging.